L Number	Hits	Search Text	DB	Time stamp
1	2	CAR same steroid same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:07
2	15	CAR same nuclear same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:08
4	7	(CAR same nuclear same receptor) and cholesS7	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:13
5	8	phenobarb$4 same cholesS7 same effect	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:14
-	5	constitutive same androstane same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:01

	U	1	Document ID	Issue Date	Pages	Title
1	☒	☐	US 20010000472 A1	20010426	14	L-ergothioneine, milk thistle, and s-adenosylmethionine for the prevention, treatment and repair of
2	☒	☐	US 6103733 A	20000815	19	Method for increasing HDL cholesterol levels using heteroaromatic phenylmethanes
3	☒	☐	US 5908861 A	19990601	26	Methods for treating inflammation and inflammatory disease using pADPRT inhibitors
4	☐	☐	US 5006526 A	19910409	5	Method of treating a vertebrate animal to reduce plasma triglycerides and cholesterol levels and to alleviate and prevent atherosclerosis
5	☐	☐	US 4645774 A	19870224	8	Aminoethoxybenzylalcohol derivatives, process for their preparation and pharmaceutical compositions containing them
6	☐	☐	US 4605785 A	19860812	9	1,1-diphenylpropanol derivatives, process for their preparation and pharmaceutical compositions containing them
7	☐	☐	US 5006526 A	19910409	5	Treatment of atherosclerosis with ergot cpds. - reduces plasma cholesterol and tri:glyceride levels
8	☐	☐	EP 115205 A	19840808	8	Alpha-phenyl-alpha-ethyl-amino:ethoxy:benzyl alcohol cpds. - useful as stimulants of liver poly:substrate mono:oxygenase enzyme system

	Current OR	Current XRef	Retrieval Classif	Inventor	S	C	P	2
1	424/725	514/398; 514/46		Henderson, Todd R. et al.	☐	☐	☐	☐
2	514/277	514/399; 514/400; 514/427; 544/333; 546/272.7; 546/343; 548/340.1; 548/346.1		Bachmann, Kenneth A. et al.	☐	☐	☐	☐
3	514/456	514/309; 514/617; 514/619; 514/622; 514/825; 514/898		Kun, Ernestt	☐	☐	☐	☐
4	514/250	514/288; 514/824		Meier, Albert H. et al.	☒	☐	☐	☐
5	514/317	514/428; 514/648; 546/241; 548/575; 564/324; 564/327		Toth, Edit et al.	☒	☐	☐	☐
6	568/649	558/389; 560/57; 562/468; 564/323; 564/326		Toth, Edit et al.	☒	☐	☐	☐
7				CINCOTTA, A H et al.	☒	☐	☐	☐
8				GOROG, S et al.	☒	☐	☐	☐

	3	4	5	Image Doc. Displayed	PT
1	☐	☐	☐	US 20010000472	☐
2	☐	☐	☐	US 6103733	☐
3	☐	☐	☐	US 5908861	☐
4	☐	☐	☐	US 5006526	☐
5	☐	☐	☐	US 4645774	☐
6	☐	☐	☐	US 4605785	☐
7	☐	☐	☐	US 5006526	☐
8	☐	☐	☐	US 4645774	☐

09/760,067

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 NEWS  3  Apr 09   BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09   ZDB will be removed from STN
 NEWS  5  Apr 19   US Patent Applications available in IFICDB, IFIPAT, and
IFIUDB
 NEWS  6  Apr 22   Records from IP.com available in CAPLUS, HCAPLUS, and
ZCAPLUS
 NEWS  7  Apr 22   BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22   Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03   New e-mail delivery for search results now available
 NEWS 10  Jun 10   MEDLINE Reload
 NEWS 11  Jun 10   PCTFULL has been reloaded
 NEWS 12  Jul 02   FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22   USAN to be reloaded July 28, 2002;
                   saved answer sets no longer valid
 NEWS 14  Jul 29   Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30   NETFIRST to be removed from STN
 NEWS 16  Aug 08   CANCERLIT reload
 NEWS 17  Aug 08   PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08   NTIS has been reloaded and enhanced
 NEWS 19  Aug 09   JAPIO to be reloaded August 18, 2002

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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 NEWS WWW      CAS World Wide Web Site (general information)
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=> s cons? (p) androstane (p) receptor (p) choles?

3 FILES SEARCHED...
L1 15 CONS? (P) ANDROSTANE (P) RECEPTOR (P) CHOLES?

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2 7 DUP REM L1 (8 DUPLICATES REMOVED)

=> d l2 total ibib kwic

L2 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 2002418126 IN-PROCESS
DOCUMENT NUMBER: 22162479 PubMed ID: 12045201
TITLE: Cholesterol and Bile Acids Regulate Xenosensor Signaling in
Drug-mediated Induction of Cytochromes P450.
AUTHOR: Handschin Christoph; Podvinec Michael; Amherd Remo; Looser Renate; Ourlin Jean-Claude; Meyer Urs A
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Klingelbergstrasse 50-70, CH-4056 Basel, Switzerland.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Aug 16) 277 (33) 29561-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20020813

AB Cytochromes P450 (CYP) **constitute** the major enzymatic system for metabolism of xenobiotics. Here we demonstrate that transcriptional activation of CYPs by the drug-sensing nuclear **receptors** pregnane X **receptor**, **constitutive androstane receptor**, and the chicken xenobiotic **receptor** (CXR) can be modulated by endogenous **cholesterol** and bile acids. Bile acids induce the chicken drug-activated CYP2H1 via CXR, whereas the hydroxylated metabolites of bile acids and oxysterols inhibit drug induction. The **cholesterol**-sensing liver X **receptor** competes with CXR, pregnane X **receptor**, or **constitutive androstane receptor** for regulation of drug-responsive

enhancers fr[redacted] chicken CYP2H1, human CYP3A4, [redacted] human CYP2B6, respectively[redacted] thus, not only **cholesterol** 7alp[redacted] hydroxylase (CYP7A1), but also drug-inducible CYPs, are diametrically affected by these **receptors**. Our findings reveal new insights into the increasingly complex network of nuclear **receptors** regulating lipid homeostasis and drug metabolism.

L2 ANSWER 2 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002276876 MEDLINE
DOCUMENT NUMBER: 22012188 PubMed ID: 12016543
TITLE: Regulation of hepatic drug metabolism: role of the nuclear receptors PXR and CAR.
AUTHOR: Liddle Christopher; Goodwin Bryan
CORPORATE SOURCE: Department of Clinical Pharmacology and Storr Liver Unit, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Westmead, Australia.. chris.liddle@wmi.usyd.edu.au
SOURCE: SEMINARS IN LIVER DISEASE, (2002) 22 (2) 115-22. Ref: 90
Journal code: 8110297. ISSN: 0272-8087.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020518
Last Updated on STN: 20020709
Entered Medline: 20020708

AB Recent advances in the molecular biology of nuclear **receptors** have revealed that the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR) are able to act as sensors for lipophilic xenobiotics, including therapeutic drugs. These **receptors** in turn regulate enzymes and transporters involved in drug metabolism and disposition in an adaptive fashion. An unexpected finding was that the PXR was able to recognize bile acids; transgenic animals lacking this **receptor** are at increased risk of bile acid-induced liver injury. These findings provide new insights into hepatic drug metabolism as well as mechanisms regulating **cholesterol** and bile acid homeostasis.

L2 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:525915 CAPLUS
DOCUMENT NUMBER: 135:127155
TITLE: Screening constitutive androstane receptor (CAR) modulators for treatment of hypercholesterolemia associated diseases
INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan
PATENT ASSIGNEE(S): Tularik Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176398P P 20000113

AB This invention provides methods that are useful for identifying therapeutic agents for the treatment of a **constitutive androstane receptor** (CAR)-mediated disorder or condition. The methods include detg. whether the candidate therapeutic agent can: interact directly with CAR, modulate CAR-mediated gene expression, decrease CAR antagonist elevation of a **cholesterol** indicator in a mammal, or decrease a **cholesterol** level indicator in a mammal with a defective CAR. Also provided are CAR agonists. The invention also provides methods for producing a transgenic mouse having a genome with a disrupted CAR allele. The invention further provides methods for treating a CAR-mediated disorder or condition such as hypercholesterolemia, lipid disorders, atherosclerosis, and cardiovascular disorders.

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(as a indicator for **cholesterol** level; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(very-low-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, **cholesterol**, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(serum; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

L2 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:817836 CAPLUS
DOCUMENT NUMBER: 136:112073
TITLE: Orphan nuclear receptors: the exotics of xenobiotics
AUTHOR(S): Xie, Wen; Evans, Ronald M.
CORPORATE SOURCE: Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SOURCE: Journal of Biological Chemistry (2001), 276(41), 37739-37742
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review discusses the mol. complexity of xenobiotics and nuclear **receptor** (NR)-mediated xenobiotic regulation. Orphan NRs play a unique role in the regulation of cytochrome P 450 (CYP) genes by

functioning as atypical pleotropic **receptors** for a remarkable diversity of xenobiotic compds. The identity of **constitutive androstane receptor** (CAR) as a xenobiotic **receptor** was first indicated by the ability of selective **androstane** metabolites to inhibit its **constitutive** activity. Similar to SXR (steroid and xenobiotic **receptor**) and its rodent ortholog PXR (pregnane X **receptor**), CAR also shows clear species-dependent ligand specificity. A combination of knockout and transgenic mouse studies revealed that activation of SXR/PXR is necessary and sufficient to both induce CYP3A enzymes and confer a resistance to toxic **cholestatic** bile acid lithocholic acid.

L2 ANSWER 5 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001514846 MEDLINE
DOCUMENT NUMBER: 21446829 PubMed ID: 11562429
TITLE: Multiple enhancer units mediate drug induction of CYP2H1 by xenobiotic-sensing orphan nuclear receptor chicken xenobiotic receptor.
AUTHOR: Handschin C; Podvinec M; Looser R; Amherd R; Meyer U A
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Basel, Switzerland.
SOURCE: MOLECULAR PHARMACOLOGY, (2001 Oct) 60 (4) 681-9. Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010920
Last Updated on STN: 20011008
Entered Medline: 20011004

AB Binding of nuclear **receptors** to drug-responsive enhancer units mediates transcriptional activation of cytochromes P-450 (P-450) by drugs and xenobiotics. In previous studies, a 264-base-pair. . . to -1408 upstream of the chicken CYP2H1 transcriptional start-site increased gene expression when activated by the chicken xenobiotic-sensing orphan nuclear **receptor** CXR. In extension of these studies, we now have functionally analyzed a second distal drug-responsive element and delimited a 643-. . . of the transcriptional start site of CYP2H1. Both PBRUs were activated by CXR after treatment with different drugs. A nuclear **receptor** binding site, a direct repeat-4 (DR-4) hexamer repeat, was identified on the 240-bp PBRU. Site-directed mutagenesis of this DR-4 abolished. . . the complex remained unaffected by unlabeled 240-bp PBRU with a mutated DR-4. In cross-species experiments, both the human xenobiotic-sensing nuclear **receptors** pregnane X **receptor** and **constitutive androstane receptor** bound to this element, suggesting sequence **conservation** between chicken and mammalian PBRUs and between the DNA binding domains of these **receptors**. Of two orphan nuclear **receptors** involved in **cholesterol** and bile acid homeostasis, only chicken liver X **receptor** (LXR) but not chicken farnesoid X **receptor** bound to the 240-bp PBRU. These results suggest that CYP2H1 induction is explained by the combined effect of multiple distal. . .

L2 ANSWER 6 OF 7 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001078235 MEDLINE
DOCUMENT NUMBER: 20545466 PubMed ID: 10967108
TITLE: Topography of nicotinic acetylcholine receptor membrane-embedded domains.
AUTHOR: Barrantes F J; Antollini S S; Blanton M P; Prieto M
CORPORATE SOURCE: Instituto de Investigaciones Bioquimicas de Bahia Blanca,

B8000FWB Bahia Blanca, Argentina.
CONTRACT NUMBER: 1RO3-TW01225-01 (FIC)
R29NS35786 (NINDS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Dec 1) 275 (48) 37333-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB The topography of nicotinic acetylcholine **receptor** (AChR) membrane-embedded domains and the relative affinity of lipids for these protein regions were studied using fluorescence methods. Intact Torpedo. . . protein and transmembrane peptides were derivatized with N-(1-pyrenyl)maleimide (PM), purified, and reconstituted into asolectin liposomes. Fluorescence mapped to proteolytic fragments **consistent** with PM labeling of cysteine residues in alphaM1, alphaM4, gammaM1, and gammaM4. The topography of the pyrene-labeled Cys residues with. . . affinity for representative lipids were determined by differential fluorescence quenching with spin-labeled derivatives of fatty acids, phosphatidylcholine, and the steroids **cholestane** and **androstane**. Different spin label lipid analogs exhibit different selectivity for the whole AChR protein and its transmembrane domains. In all cases. . . of the presence of a substantial amount of non-helical structure, and/or of kinks attributable to the occurrence of the evolutionarily **conserved** proline residues. The latter is a striking feature of M1 in the AChR and all members of the rapid ligand-gated. . .

L2 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:526330 BIOSIS
DOCUMENT NUMBER: PREV200000526330
TITLE: Transcriptional control of hepatocanalicular transporter gene expression.
AUTHOR(S): Muller, Michael (1)
CORPORATE SOURCE: (1) Division of Gastroenterology and Hepatology, University
Hospital Groningen, Hanzeplein 1, NL-9713GZ, Groningen Netherlands
SOURCE: Seminars in Liver Disease, (2000) Vol. 20, No. 3, pp. 323-337. print.
ISSN: 0272-8087.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
IT . . .
Molecular Genetics (Biochemistry and Molecular Biophysics); Digestive System (Ingestion and Assimilation)
IT Chemicals & Biochemicals
BSEP: bile salt transporter protein; **constitutive androstane receptor**; farnesoid X **receptors**: bile acid **receptor**; hepatocanalicular transport genes: transcriptional expression control; liver X **receptors**: dietary **cholesterol** sensors; multidrug resistance protein-1; multidrug resistance protein-2; multidrug resistance protein-3: basolateral anionic conjugate transporter, bile salt transporter; nuclear factor-kappa-B: stress response factor; nuclear ligand-activated **receptors**; p53: stress response factor; peroxisome proliferator activated **receptor**-alpha; pregnane X **receptor**: steroid binding activity, xenobiotic binding activity; sterol-responsive element binding proteins; transcription factors; mouse hepatic ABC transporter gene (Muridae): transcription

regulation

=> s cyp2b (p) cholesterol

L3 10 CYP2B (P) CHOLESTEROL

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 4 DUP REM L3 (6 DUPLICATES REMOVED)

=> d l4 total ibib kwic

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:257045 CAPLUS
DOCUMENT NUMBER: 133:56561
TITLE: Differential suppression of liver-specific genes in regenerating rat liver induced by extended hepatectomy
AUTHOR(S): Kurumiya, Yasuhiro; Nozawa, Katsura; Sakaguchi, Kenji; Nagino, Masato; Nimura, Yuji; Yoshida, Shonen
CORPORATE SOURCE: First Department of Surgery, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Nagoya, 466-8550, Japan
SOURCE: Journal of Hepatology (2000), 32(4), 636-644
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
ST serum albumin apolipoprotein phosphoenolpyruvate carboxykinase liver regeneration; PEPCK OTC **CYP2B** ODC gene hepatocyte proliferation; ornithine transcarbamylase cytochrome jun PCNA liver regeneration; HGF ornithine decarboxylase thymidine kinase hepatocyte proliferation; TK proliferating cell nuclear antigen DNA polymerase regeneration; actin GAPDH haptoglobin macroglobulin liver regeneration; blood **cholesterol** glucose bilirubin liver regeneration

L4 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000004580 MEDLINE
DOCUMENT NUMBER: 20004580 PubMed ID: 10534307
TITLE: Effect of a ligand selective for peripheral benzodiazepine receptors on the expression of rat hepatic P-450 cytochromes: assessment of the effect in vivo and in a hepatocyte culture system.
AUTHOR: Yamada H; Matsuki Y; Yamaguchi T; Oguri K
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.
SOURCE: DRUG METABOLISM AND DISPOSITION, (1999 Nov) 27 (11) 1242-7.
Journal code: 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB The peripheral benzodiazepine receptor plays a role in the translocation

of **cholesterol** into mitochondria where steroidogenesis occurs. Sterols have been suggested to be involved in the regulation of the cytochrome P-450 (CYP)2B subfamily as the endogenous suppressor of this CYP. To investigate the role of **cholesterol** metabolites on the expression of CYPs, the effect of PK11195, a specific ligand of the peripheral benzodiazepine receptor and a stimulator of **cholesterol** transportation, on CYP expression was examined in rats in vivo and in cultured hepatocytes. As judged by the change in testosterone metabolic activity catalyzed by liver microsomes, i.p. injection of PK11195 into rats increased the **CYP2B** subfamily significantly. A trend in the induction of the CYP2A1, 2C11, and 3A isozymes was also observed. When PK11195 was. . . the magnitude of the effect was much greater than that observed in vivo. The inductive effect of PK11195 toward the **CYP2B** and 3A subfamilies was 2.3- and 6.5-fold greater, respectively, than that with phenobarbital. The inductive effect of PK11195 was confirmed. . . expression of these CYPs. This observation suggests that, if certain sterols play a role in the suppressive control of the **CYP2B** subfamily, they are produced in organelles other than the mitochondria.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:635125 CAPLUS
DOCUMENT NUMBER: 129:339755
TITLE: Regulation of rat hepatic cytochrome P450 expression by sterol biosynthesis inhibition: inhibitors of squalene synthase are potent inducers of CYP2B expression in primary cultured rat hepatocytes and rat liver
AUTHOR(S): Kocarek, Thomas A.; Kraniak, Janice M.; Reddy, Anita B.
CORPORATE SOURCE: Institute of Chemical Toxicology, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Molecular Pharmacology (1998), 54(3), 474-484
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 57-88-5, **Cholesterol**, biological studies 79-63-0, Lanosterol 111-02-4, Squalene 9028-35-7, 3-Hydroxy-3-methylglutaryl CoA reductase 96595-04-9, Pentoxyresorufin O-dealkylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors of squalene synthase as inducers of **CYP2B** expression in primary cultured rat hepatocytes and rat liver)

L4 ANSWER 4 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998337723 MEDLINE
DOCUMENT NUMBER: 98337723 PubMed ID: 9674966
TITLE: Marked inhibition of hepatic cytochrome P450 activity in cholesterol-induced atherosclerosis in rabbits.
AUTHOR: Irizar A; Ioannides C
CORPORATE SOURCE: Molecular Toxicology Group, School of Biological Sciences, University of Surrey, Guildford, UK.
SOURCE: TOXICOLOGY, (1998 Apr 3) 126 (3) 179-93.
Journal code: 0361055. ISSN: 0300-483X.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980806
AB . . . and of other enzyme systems, in hepatic and extrahepatic tissues of rabbits rendered atherosclerotic by the dietary administration of 1%

cholesterol diets for 8 weeks. Individual cytochrome P450 proteins were monitored using diagnostic substrates and immunologically in Western blot analysis. The. . . determined immunologically, no major differences were evident between the control and the atherosclerotic rabbits. In vitro studies indicated that neither **cholesterol** nor palm oil inhibited cytochrome P450 activity. The effects of **cholesterol** treatment leading to atherosclerosis on kidney, heart and lung cytochrome P450 activities were isoform- and tissue-specific; no change was evident. . . in the heart activities, but in the lung and kidney cytochrome P450 activities were clearly modulated by the treatment with **cholesterol**. Apoprotein levels did not always parallel the changes in activities. Western blot analysis of aortic cytochromes P450 revealed that administration of **cholesterol**-rich diets enhanced **CYP2B** and CYP3A apoprotein levels. **Cholesterol** feeding to rabbits gave rise to a marked decrease in hepatic glutathione S-transferase activity but did not influence glutathione reductase. . . same treatment had no effect on catalase, glutathione peroxidase and superoxide dismutase. It is concluded that treatment of rabbits with **cholesterol**-rich diets leading to atherosclerosis gives rise to profound changes in the expression of cytochrome P450 proteins in the liver and. . .

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	28.23	28.44

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 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and
IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and
ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 09  JAPIO to be reloaded August 18, 2002

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> s constitutive (p) androstane (p) receptor

L1          219 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR

=> s constitutive (p) androstane (p) receptor (p) screen?

L2           17 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) SCREEN?

=> s constitutive (p) androstane (p) receptor (p) screen? (p) compound

L3            4 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) SCREEN? (P)
COMPOUN
                D

=> s constitutive (p) androstane (p) receptor (p) assay (p) compound

L4            8 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) ASSAY (P) COMPOUND

=> s l2 and l3 and l4

L5            0 L2 AND L3 AND L4

=> s l2 or l3 or l4

L6           25 L2 OR L3 OR L4

=> dup rem l6

PROCESSING COMPLETED FOR L6
L7           10 DUP REM L6 (15 DUPLICATES REMOVED)

=> d l7 total ibib kwic


L7   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:240977  CAPLUS
DOCUMENT NUMBER:          136:274330
TITLE:                    Sequence of a human cytochrome P450 3A7 gene promoter
                          region and uses in drug screening
INVENTOR(S):              Berkenstam, Anders; Bertilsson, Goeran; Blomquist,
                          Patrik
PATENT ASSIGNEE(S):       Biovitrum AB, Swed.
SOURCE:                   PCT Int. Appl., 39 pp.
                          CODEN: PIXXD2
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024918	A1	20020328	WO 2001-SE2007	20010919

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 2000-3393 A 20000922
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

AB The present invention relates to an isolated human cytochrome P 450 3A7 (CYP3A7) promoter region, and identifies the pregnane activated **receptor** (PAR) responsive element in the CYP3A7 promoter region. The invention further discloses that **constitutive androstane receptor** (CAR) can upregulate the CYP3A7 promoter via xenobiotic response element (XREM). The invention also relates to **screening** methods for agents modulating the expression of CYP3A7, such agents being potentially useful in modulating metab. of endogenous and/or exogenous **compds**., drug interaction, toxicity and/or bioavailability of drugs.

ST sequence human cytochrome P450 3A7 CYP3A7 promoter drug **screening** ; gene CYP3A7 promoter pregnane activated **receptor** responsive element PAR; promoter CYP3A7 **constitutive androstane receptor** CAR regulation

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CAR (**constitutive androstane receptor**); sequence of a human cytochrome P 450 3A7 promoter region and uses in drug **screening**)

L7 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002089312 MEDLINE
DOCUMENT NUMBER: 21659720 PubMed ID: 11706036
TITLE: Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor.
AUTHOR: Kast Heidi R; Goodwin Bryan; Tarr Paul T; Jones Stacey A; Anisfeld Andrew M; Stoltz Catherine M; Tontonoz Peter; Kliewer Steve; Willson Timothy M; Edwards Peter A
CORPORATE SOURCE: Department of Biological Chemistry and Medicine, UCLA, Los Angeles, California 90095, USA.
CONTRACT NUMBER: HL30568 (NHLBI)
HL68445 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 2908-15.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020131
Last Updated on STN: 20020226

Entered Medline: 20020225

AB The multidr[redacted]resistance-associated protein 2 [redacted]MRP2, ABCC2), mediates the efflux of several conjugated **compounds** across the apical membrane of the hepatocyte into the bile canaliculi. We identified MRP2 in a **screen** designed to isolate genes that are regulated by the farnesoid X-activated **receptor** (FXR, NR1H4). MRP2 mRNA levels were induced following treatment of human or rat hepatocytes with either naturally occurring (chenodeoxycholic acid) or synthetic (GW4064) FXR ligands. In addition, we have shown that MRP2 expression is regulated by the pregnane X **receptor** (PXR, NR1I2) and **constitutive androstane receptor** (CAR, NR1I3). Thus, treatment of rodent hepatocytes with PXR or CAR agonists results in a robust induction of MRP2 mRNA. . . . 8 nucleotides (ER-8). PXR, CAR, and FXR bound with high affinity to this element as heterodimers with the retinoid X **receptor** alpha (RXRalpha, NR2B1). Luciferase reporter gene constructs containing 1 kb of the rat MRP2 promoter were prepared and transiently transfected. . . . conferring PXR, CAR, and FXR responsiveness on a heterologous thymidine kinase promoter. Mutation of the ER-8 element abolished the nuclear **receptor** response. These studies demonstrate that MRP2 is regulated by three distinct nuclear **receptor** signaling pathways that converge on a common response element in the 5'-flanking region of this gene.

L7 ANSWER 3 OF 10 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002374737 MEDLINE
DOCUMENT NUMBER: 22116398 PubMed ID: 12120277
TITLE: PXR, CAR and drug metabolism.
AUTHOR: Willson Timothy M; Kliewer Steven A
CORPORATE SOURCE: GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, North Carolina 27709, USA.. tmw20653@gsk.com
SOURCE: Nat Rev Drug Discov, (2002 Apr) 1 (4) 259-66. Ref: 103
Journal code: 101124171.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020718
Last Updated on STN: 20020731
Entered Medline: 20020730

AB . . . harmful chemicals are also involved in drug metabolism, and can cause adverse drug-drug interactions. Two closely related orphan nuclear hormone **receptors**--the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR)--have recently emerged as transcriptional regulators of cytochrome P450 expression that couple xenobiotic exposure to oxidative metabolism. In this review,. . . examination of the roles of PXR and CAR as xenobiotic sensors, and discuss the application of this knowledge to toxicological **screening** in drug discovery.

L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:713686 CAPLUS
DOCUMENT NUMBER: 135:267693
TITLE: **Constitutive androstane receptor** ligand **screening** using method involving clotrimazole
INVENTOR(S): Collins, Jon L.; Parks, Derek J.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001071361	A2	20010927	WO 2001-US9233	20010322
WO 2001071361	A3	20020606		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2001055815	A1	20011227	US 2001-814569	20010322

PRIORITY APPLN. INFO.: US 2000-191493P P 20000323

TI **Constitutive androstane receptor** ligand **screening** using method involving clotrimazole

ST **constitutive androstane receptor** ligand **screening** clotrimazole; human sequence **constitutive androstane receptor** LBD fragment

IT Androgen **receptors**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CAR (**constitutive androstane receptor**); **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Spheres
(beads, solid support; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to bead solid support)

IT Drug delivery systems
Drug **screening**
Protein sequences
(**constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Biotinylation
(**constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to coated bead solid support)

IT Fusion proteins (chimeric proteins)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**constitutive androstane receptor** ligand-binding domain; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Protein motifs
(ligand-binding domain of **constitutive androstane receptor**; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Avidins
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(solid support bead coating; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to coated bead solid support)

IT 363631-04-3
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT 23593-75-1, Clotrimazole 23593-75-1D, Clotrimazole, radiolabeled
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**constitutive androstane receptor** ligand **screening** using method involving clotrimazole)
IT 58-85-5, Biotin 9013-20-1, Streptavidin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(solid support bead coating; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to coated bead solid support)
IT 363593-56-0 364059-93-8
RL: PRP (Properties)
(unclaimed sequence; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:525915 CAPLUS
DOCUMENT NUMBER: 135:127155
TITLE: **Screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia associated diseases
INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan
PATENT ASSIGNEE(S): Tularik Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176398P P 20000113
TI **Screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia associated diseases
ST **constitutive androstane receptor** CAR modulator **screening** hypercholesterolemia
IT Transcriptional regulation
(CAR-mediated; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CAR-responsive, DR-4 or DR-5; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(CAR.beta.; **screening constitutive androstane receptor** (CAR) modulators for treatment of

hypercholesterolemia assocd. diseases)

IT Estrogen **receptors**
Glucocorticoid **receptors**
Mineralocorticoid **receptors**
Progesterone **receptors**
Retinoid **receptors**
Thyroid hormone **receptors**
Vitamin D **receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA-binding domain from; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GAL4, DNA-binding domain from; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SRC-1 (steroid **receptor** coactivator-1), **receptor** binding domain of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Antiarteriosclerotics
(antiatherosclerotics; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(as a indicator for cholesterol level; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipids, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(blood; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Androgen **receptors**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**constitutive**, CAR.alpha. or CAR.beta.; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Mutation
(deletion, of CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Resonance fluorescence
(energy transfer; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Fluorescent indicators
Isotope indicators
(for labeling CAR ligands; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Proteins, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(green fluorescent, gene for, as reporter; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR)

modulators for treatment of hypercholesterolemia assocd. diseases)
IT Mutation
(insertion, of CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Peptides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(labeled; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic disorders, treatment of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Fluorometry
(polarization; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Cardiovascular agents
Drug **screening**
Molecular cloning
(**screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Reporter gene
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Peptides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensor; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Mammal (Mammalia)
Mouse
(transgenic, CAE allele-disrupted; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Hypercholesterolemia
(treatment of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(very-low-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT 198705-46-3 301654-35-3 338961-03-8 351153-65-6 351153-66-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(CAR agonist; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)
IT 1153-51-1, 5.alpha.-androst-16-en-3.alpha.-ol 7657-50-3 95118-94-8, 5.alpha.-Androst-16-en-3.alpha.-ol acetate
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(CAR ligand; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 225916-35-8
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 9001-78-9, Alkaline phosphatase 9014-00-0, luciferase 9031-11-2, .beta.-Galactosidase 9040-07-7, Chloramphenicol acetyltransferase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(gene for, as reporter; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 81-88-9
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(labeled peptide; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 76150-91-9, 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(ligand for CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 128-23-4, 5.beta.-pregnan-3,20 dione
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(ligand for CAR.alpha.; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 1404-04-2, neomycin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(resistance gene as marker gene; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, cholesterol, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(serum; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 351237-24-6, 4: PN: WO0151045 SEQID: 4 unclaimed DNA 351237-25-7, 5: PN:
WO0151045 SEQID: 5 unclaimed DNA 351237-26-8, 6: PN: WO0151045 SEQID: 6 unclaimed DNA 351237-27-9, 8: PN: WO0151045 SEQID: 8 unclaimed DNA 351237-29-1 351237-30-4
RL: PRP (Properties)
(unclaimed nucleotide sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 197731-92-3 351237-22-4 351237-23-5 351237-28-0
RL: PRP (Properties)
(unclaimed protein sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

L7 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:168249 CAPLUS
DOCUMENT NUMBER: 134:217982
TITLE: Chromatin-based RAR/RXR heterodimer-regulated transcription system and its use in screening for transcription modulators
INVENTOR(S): Chambon, Pierre; Dilworth, F. Jeffrey; Fromental-Ramain, Catherine
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale, Fr.; Centre National de la Recherche Scientifique; Universite Louis Pasteur; Bristol-Myers Squibb Company
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016597	A1	20010308	WO 1999-US20018	19990901

W: AU, CA, IL, JP, MX, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT
IT **Receptors**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(CAR (**constitutive androstane receptors**);
chromatin-based RAR/RXR heterodimer-regulated transcription system and its use in **screening** for transcription modulators)

L7 ANSWER 7 OF 10 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001475469 MEDLINE
DOCUMENT NUMBER: 21410114 PubMed ID: 11518807
TITLE: Conservation of signaling pathways of xenobiotic-sensing orphan nuclear receptors, chicken xenobiotic receptor, constitutive androstane receptor, and pregnane X receptor, from birds to humans.
AUTHOR: Handschin C; Podvinec M; Stockli J; Hoffmann K; Meyer U A
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, CH-4056 Basel, Switzerland.
SOURCE: MOLECULAR ENDOCRINOLOGY, (2001 Sep) 15 (9) 1571-85.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20020125
Entered Medline: 20020114

AB Chicken xenobiotic **receptor**, pregnane X **receptor**, and **constitutive androstane receptor** are orphan nuclear **receptors** that have recently been discovered to regulate drug- and steroid-mediated induction of hepatic cytochromes P450 (CYP). This induction is part. . . experiments in the chicken hepatoma cell line LMH that suggest evolutionary conservation of the signaling pathways triggered by pregnane X **receptor**, **constitutive androstane receptor**, and chicken xenobiotic **receptor**. Thus, the phenobarbital-inducible enhancer units of the mouse Cyp2b10, rat CYP2B2, and human CYP2B6 genes were activated in reporter gene **assays** by the same **compounds** that activate the chicken CYP2H1 phenobarbital-inducible enhancer units.

Chicken xenobiotic **receptor**, pregnane X **receptor**, and **constitutive androstane receptor** all bound to the CYP2H1 phenobarbital-inducible enhancer units in gel-shift experiments. In CV-1 cell transactivation **assays**, mammalian pregnane X **receptors** activate the chicken phenobarbital-inducible enhancer units to the same extent as does chicken xenobiotic **receptor**, each **receptor** maintaining its species-specific ligand spectrum. To assess the reported role of protein phosphorylation in drug-mediated induction, we treated LMH cells. . . comparable to those seen on CYP2Bs and CYP3As in mammalian primary hepatocyte cultures. These results indicate that closely related nuclear **receptors**, transcription factors, and signaling pathways are mediating the transcriptional activation of multiple genes by xenobiotics in chicken, rodents, and man.

L7 ANSWER 8 OF 10 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000270219 MEDLINE
DOCUMENT NUMBER: 20270219 PubMed ID: 10748001
TITLE: Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands.
AUTHOR: Moore L B; Parks D J; Jones S A; Bledsoe R K; Consler T G; Stimmel J B; Goodwin B; Liddle C; Blanchard S G; Willson T M; Collins J L; Kliewer S A
CORPORATE SOURCE: Department of Molecular Endocrinology, Glaxo Wellcome Research and Development, Research Triangle Park, North Carolina 27709, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 19) 275 (20) 15122-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB Xenobiotics induce the transcription of cytochromes P450 (CYPs) 2B and 3A through the **constitutive androstane receptor** (CAR; NR1I3) and pregnane X **receptor** (PXR; NR1I2), respectively. In this report, we have systematically compared a series of xenobiotics and natural steroids for their effects. . . on mouse and human CAR and PXR. Our results demonstrate dual regulation of PXR and CAR by a subset of **compounds** that affect CYP expression. Moreover, there are marked pharmacological differences between the mouse (m) and human (h) orthologs of both. . . PXR. Similarly, the PXR activator clotrimazole is a potent deactivator of hCAR. Using radioligand binding and fluorescence resonance energy transfer **assays**, we demonstrate that several of the **compounds** that regulate mouse and human CAR, including natural steroids, bind directly to the **receptors**. Our results suggest that CAR, like PXR, is a steroid **receptor** that is capable of recognizing structurally diverse **compounds**. Moreover, our findings underscore the complexity in the physiologic response to xenobiotics.

L7 ANSWER 9 OF 10 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001305626 MEDLINE
DOCUMENT NUMBER: 20525078 PubMed ID: 11075820
TITLE: Estrogen activation of the nuclear orphan receptor CAR (constitutive active receptor) in induction of the mouse Cyp2b10 gene.
AUTHOR: Kawamoto T; Kakizaki S; Yoshinari K; Negishi M

CORPORATE SOURCE: Pharmacogenetics Section, Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (2000 Nov) 14 (11) 1897-905. Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB The nuclear orphan **receptor** CAR (constitutively active **receptor** or **constitutive androstane receptor**) can be activated in response to xenochemical exposure, such as activation by phenobarbital of a response element called NR1 found in the CYP2B gene. Here various steroids were **screened** for potential endogenous chemicals that may activate CAR, using the NR1 enhancer and Cyp2b10 induction in transfected HepG2 cell and/or. . . is an effective activator of CAR in both female and male mice, suggesting a biological and/or toxicological role of this **receptor** in estrogen metabolism. In addition to mouse CAR, estrogens activated rat CAR, whereas human CAR did not respond well to. . .

L7 ANSWER 10 OF 10 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998322543 MEDLINE
DOCUMENT NUMBER: 98322543 PubMed ID: 9658407
TITLE: Molecular cloning of xSRC-3, a novel transcription coactivator from Xenopus, that is related to AIB1, p/CIP, and TIF2.
AUTHOR: Kim H J; Lee S K; Na S Y; Choi H S; Lee J W
CORPORATE SOURCE: College of Pharmacy, Chonnam National University, Kwangju, South Korea.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1998 Jul) 12 (7) 1038-47. Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981005

AB Nuclear **receptors** regulate transcription by binding to specific DNA response elements of target genes. Herein, we report the molecular cloning and characterization of a novel Xenopus cDNA encoding a transcription coactivator xSRC-3 by using retinoid X **receptor** (RXR) as a bait in the yeast two-hybrid **screening**. It belongs to a growing coactivator family that includes a steroid **receptor** coactivator amplified in breast cancer (AIB1), p300/ CREB-binding protein (CBP)-interacting protein (p/ CIP), and transcriptional intermediate factor 2 (TIF2). It also interacts with a series of nuclear **receptors** including retinoic acid **receptor** (RAR), thyroid hormone **receptor** (TR), and orphan nuclear **receptors** [hepatocyte nuclear **receptor** 4 (HNF4) and **constitutive androstane receptor** (CAR)]. However, it does not interact with small heterodimer partner (SHP), an orphan nuclear **receptor** known to antagonize ligand-dependent transactivation of other nuclear **receptors**. In CV-1 cells, cotransfection of xSRC-3 differentially stimulates ligand-induced transactivation of RXR, TR, and RAR in a dose-dependent manner.

Interestingly, . . . and early stages of oocyte development, suggesting that studies of xSRC-3 may lead to better understanding of the roles nuclear **receptors** play in oocyte development as well as liver-specific gene expression.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	38.98	39.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.62	-0.62

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 08:29:40 ON 14 AUG 2002

FILE 'BIOSIS' ENTERED AT 08:29:40 ON 14 AUG 2002
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=> s cons? (p) androstane (p) receptor (p) choles?

3 FILES SEARCHED...
L1 15 CONS? (P) ANDROSTANE (P) RECEPTOR (P) CHOLES?

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2 7 DUP REM L1 (8 DUPLICATES REMOVED)

=> d l2 total ibib kwic

L2 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 2002418126 IN-PROCESS
DOCUMENT NUMBER: 22162479 PubMed ID: 12045201
TITLE: Cholesterol and Bile Acids Regulate Xenosensor Signaling in Drug-mediated Induction of Cytochromes P450.
AUTHOR: Handschin Christoph; Podvinec Michael; Amherd Remo; Looser Renate; Ourlin Jean-Claude; Meyer Urs A
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Klingelbergstrasse 50-70, CH-4056 Basel, Switzerland.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Aug 16) 277 (33) 29561-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20020813

AB Cytochromes P450 (CYP) **constitute** the major enzymatic system for metabolism of xenobiotics. Here we demonstrate that transcriptional activation of CYPs by the drug-sensing nuclear **receptors** pregnane X **receptor**, **constitutive androstane receptor**, and the chicken xenobiotic **receptor** (CXR) can be modulated by endogenous **cholesterol** and bile acids. Bile acids induce the chicken drug-activated CYP2H1 via CXR, whereas the hydroxylated metabolites of bile acids and oxysterols inhibit drug induction. The **cholesterol**-sensing liver X **receptor** competes with CXR, pregnane X **receptor**, or **constitutive androstane receptor** for regulation of drug-responsive

enhancers from chicken CYP2H1, human CYP3A4, or human CYP2B6, respectively. Thus, not only **cholesterol** 7alpha-hydroxylase (CYP7A1), but also drug-inducible CYPs, are diametrically affected by these **receptors**. Our findings reveal new insights into the increasingly complex network of nuclear **receptors** regulating lipid homeostasis and drug metabolism.

L2 ANSWER 2 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002276876 MEDLINE
DOCUMENT NUMBER: 22012188 PubMed ID: 12016543
TITLE: Regulation of hepatic drug metabolism: role of the nuclear receptors PXR and CAR.
AUTHOR: Liddle Christopher; Goodwin Bryan
CORPORATE SOURCE: Department of Clinical Pharmacology and Storr Liver Unit, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Westmead, Australia.. chris.liddle@wmi.usyd.edu.au
SOURCE: SEMINARS IN LIVER DISEASE, (2002) 22 (2) 115-22. Ref: 90
Journal code: 8110297. ISSN: 0272-8087.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020518
Last Updated on STN: 20020709
Entered Medline: 20020708

AB Recent advances in the molecular biology of nuclear **receptors** have revealed that the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR) are able to act as sensors for lipophilic xenobiotics, including therapeutic drugs. These **receptors** in turn regulate enzymes and transporters involved in drug metabolism and disposition in an adaptive fashion. An unexpected finding was that the PXR was able to recognize bile acids; transgenic animals lacking this **receptor** are at increased risk of bile acid-induced liver injury. These findings provide new insights into hepatic drug metabolism as well as mechanisms regulating **cholesterol** and bile acid homeostasis.

L2 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:525915 CAPLUS
DOCUMENT NUMBER: 135:127155
TITLE: Screening constitutive androstane receptor (CAR) modulators for treatment of hypercholesterolemia associated diseases
INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan
PATENT ASSIGNEE(S): Tularik Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-176398P P 20000113

AB This invention provides methods that are useful for identifying therapeutic agents for the treatment of a **constitutive androstane receptor** (CAR)-mediated disorder or condition. The methods include detg. whether the candidate therapeutic agent can: interact directly with CAR, modulate CAR-mediated gene expression, decrease CAR antagonist elevation of a **cholesterol** indicator in a mammal, or decrease a **cholesterol** level indicator in a mammal with a defective CAR. Also provided are CAR agonists. The invention also provides methods for producing a transgenic mouse having a genome with a disrupted CAR allele. The invention further provides methods for treating a CAR-mediated disorder or condition such as hypercholesterolemia, lipid disorders, atherosclerosis, and cardiovascular disorders.

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(as a indicator for **cholesterol** level; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(very-low-d., as **cholesterol** indicator; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, **cholesterol**, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(serum; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

L2 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:817836 CAPLUS
DOCUMENT NUMBER: 136:112073
TITLE: Orphan nuclear receptors: the exotics of xenobiotics
AUTHOR(S): Xie, Wen; Evans, Ronald M.
CORPORATE SOURCE: Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SOURCE: Journal of Biological Chemistry (2001), 276(41), 37739-37742
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review discusses the mol. complexity of xenobiotics and nuclear **receptor** (NR)-mediated xenobiotic regulation. Orphan NRs play a unique role in the regulation of cytochrome P 450 (CYP) genes by functioning as atypical pleotropic **receptors** for a remarkable

diversity of xenobiotic compds. The identity of **constitutive androstane receptor** (CAR) as a xenobiotic **receptor** was first indicated by the ability of selective **androstane** metabolites to inhibit its **constitutive** activity. Similar to SXR (steroid and xenobiotic **receptor**) and its rodent ortholog PXR (pregnane X **receptor**), CAR also shows clear species-dependent ligand specificity. A combination of knockout and transgenic mouse studies revealed that activation of SXR/PXR is necessary and sufficient to both induce CYP3A enzymes and confer a resistance to toxic **cholestatic** bile acid lithocholic acid.

L2 ANSWER 5 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001514846 MEDLINE
DOCUMENT NUMBER: 21446829 PubMed ID: 11562429
TITLE: Multiple enhancer units mediate drug induction of CYP2H1 by xenobiotic-sensing orphan nuclear receptor chicken xenobiotic receptor.
AUTHOR: Handschin C; Podvinec M; Looser R; Amherd R; Meyer U A
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Basel, Switzerland.
SOURCE: MOLECULAR PHARMACOLOGY, (2001 Oct) 60 (4) 681-9. Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010920
Last Updated on STN: 20011008
Entered Medline: 20011004

AB Binding of nuclear **receptors** to drug-responsive enhancer units mediates transcriptional activation of cytochromes P-450 (P-450) by drugs and xenobiotics. In previous studies, a 264-base-pair. . . to -1408 upstream of the chicken CYP2H1 transcriptional start-site increased gene expression when activated by the chicken xenobiotic-sensing orphan nuclear **receptor** CXR. In extension of these studies, we now have functionally analyzed a second distal drug-responsive element and delimited a 643-. . . of the transcriptional start site of CYP2H1. Both PBRUs were activated by CXR after treatment with different drugs. A nuclear **receptor** binding site, a direct repeat-4 (DR-4) hexamer repeat, was identified on the 240-bp PBRU. Site-directed mutagenesis of this DR-4 abolished. . . the complex remained unaffected by unlabeled 240-bp PBRU with a mutated DR-4. In cross-species experiments, both the human xenobiotic-sensing nuclear **receptors** pregnane X **receptor** and **constitutive androstane receptor** bound to this element, suggesting sequence **conservation** between chicken and mammalian PBRUs and between the DNA binding domains of these **receptors**. Of two orphan nuclear **receptors** involved in **cholesterol** and bile acid homeostasis, only chicken liver X **receptor** (LXR) but not chicken farnesoid X **receptor** bound to the 240-bp PBRU. These results suggest that CYP2H1 induction is explained by the combined effect of multiple distal. . .

L2 ANSWER 6 OF 7 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001078235 MEDLINE
DOCUMENT NUMBER: 20545466 PubMed ID: 10967108
TITLE: Topography of nicotinic acetylcholine receptor membrane-embedded domains.
AUTHOR: Barrantes F J; Antollini S S; Blanton M P; Prieto M
CORPORATE SOURCE: Instituto de Investigaciones Bioquimicas de Bahia Blanca, B8000FWB Bahia Blanca, Argentina.
CONTRACT NUMBER: 1RO3-TW01225-01 (FIC)
R29NS35786 (NINDS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Dec 1) 275 (48)

37333-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB The topography of nicotinic acetylcholine **receptor** (AChR) membrane-embedded domains and the relative affinity of lipids for these protein regions were studied using fluorescence methods. Intact Torpedo. . . protein and transmembrane peptides were derivatized with N-(1-pyrenyl)maleimide (PM), purified, and reconstituted into asolectin liposomes. Fluorescence mapped to proteolytic fragments **consistent** with PM labeling of cysteine residues in alphaM1, alphaM4, gammaM1, and gammaM4. The topography of the pyrene-labeled Cys residues with. . . affinity for representative lipids were determined by differential fluorescence quenching with spin-labeled derivatives of fatty acids, phosphatidylcholine, and the steroids **cholestane** and **androstane**. Different spin label lipid analogs exhibit different selectivity for the whole AChR protein and its transmembrane domains. In all cases. . . of the presence of a substantial amount of non-helical structure, and/or of kinks attributable to the occurrence of the evolutionarily **conserved** proline residues. The latter is a striking feature of M1 in the AChR and all members of the rapid ligand-gated. . .

L2 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:526330 BIOSIS
DOCUMENT NUMBER: PREV200000526330
TITLE: Transcriptional control of hepatocanalicular transporter gene expression.
AUTHOR(S): Muller, Michael (1)
CORPORATE SOURCE: (1) Division of Gastroenterology and Hepatology, University Hospital Groningen, Hanzeplein 1, NL-9713GZ, Groningen Netherlands
SOURCE: Seminars in Liver Disease, (2000) Vol. 20, No. 3, pp. 323-337. print.
ISSN: 0272-8087.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English

IT . . .
Molecular Genetics (Biochemistry and Molecular Biophysics); Digestive System (Ingestion and Assimilation)

IT Chemicals & Biochemicals
BSEP: bile salt transporter protein; **constitutive androstane receptor**; farnesoid X **receptors**: bile acid **receptor**; hepatocanalicular transport genes: transcriptional expression control; liver X **receptors**: dietary **cholesterol** sensors; multidrug resistance protein-1; multidrug resistance protein-2; multidrug resistance protein-3: basolateral anionic conjugate transporter, bile salt transporter; nuclear factor-kappa-B: stress response factor; nuclear ligand-activated **receptors**; p53: stress response factor; peroxisome proliferator activated **receptor**-alpha; pregnane X **receptor**: steroid binding activity, xenobiotic binding activity; sterol-responsive element binding proteins; transcription factors; mouse hepatic ABC transporter gene (Muridae): transcription regulation

=> s cyp2b (p) cholesterol

L3 10 CYP2B (P) CHOLESTEROL

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 4 DUP REM L3 (6 DUPLICATES REMOVED)

=> d l4 total ibib kwic

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:257045 CAPLUS
DOCUMENT NUMBER: 133:56561
TITLE: Differential suppression of liver-specific genes in regenerating rat liver induced by extended hepatectomy
AUTHOR(S): Kurumiya, Yasuhiro; Nozawa, Katsura; Sakaguchi, Kenji; Nagino, Masato; Nimura, Yuji; Yoshida, Shonen
CORPORATE SOURCE: First Department of Surgery, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Nagoya, 466-8550, Japan
SOURCE: Journal of Hepatology (2000), 32(4), 636-644
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST serum albumin apolipoprotein phosphoenolpyruvate carboxykinase liver regeneration; PEPCK OTC **CYP2B** ODC gene hepatocyte proliferation; ornithine transcarbamylase cytochrome jun PCNA liver regeneration; HGF ornithine decarboxylase thymidine kinase hepatocyte proliferation; TK proliferating cell nuclear antigen DNA polymerase regeneration; actin GAPDH haptoglobin macroglobulin liver regeneration; blood **cholesterol** glucose bilirubin liver regeneration

L4 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000004580 MEDLINE
DOCUMENT NUMBER: 20004580 PubMed ID: 10534307
TITLE: Effect of a ligand selective for peripheral benzodiazepine receptors on the expression of rat hepatic P-450 cytochromes: assessment of the effect in vivo and in a hepatocyte culture system.
AUTHOR: Yamada H; Matsuki Y; Yamaguchi T; Oguri K
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.
SOURCE: DRUG METABOLISM AND DISPOSITION, (1999 Nov) 27 (11) 1242-7.
Journal code: 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124

AB The peripheral benzodiazepine receptor plays a role in the translocation of **cholesterol** into mitochondria where steroidogenesis occurs. Sterols have been suggested to be involved in the regulation of the cytochrome P-450 (CYP)2B subfamily as the endogenous suppressor of this CYP. To investigate the role of **cholesterol** metabolites on the expression of CYPs, the effect of PK11195, a specific ligand of the peripheral benzodiazepine receptor and a stimulator of **cholesterol** transportation, on CYP expression was examined in rats in vivo and in cultured hepatocytes. As judged by the change in testosterone metabolic

activity catalyzed by liver microsomes, i.p. injection of PK11195 into rats increased the **CYP2B** subfamily significantly. A trend in the induction of the CYP2A1, 2C11, and 3A isozymes was also observed. When PK11195 was. . . the magnitude of the effect was much greater than that observed in vivo. The inductive effect of PK11195 toward the **CYP2B** and 3A subfamilies was 2.3- and 6.5-fold greater, respectively, than that with phenobarbital. The inductive effect of PK11195 was confirmed. . . expression of these CYPs. This observation suggests that, if certain sterols play a role in the suppressive control of the **CYP2B** subfamily, they are produced in organelles other than the mitochondria.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:635125 CAPLUS
DOCUMENT NUMBER: 129:339755
TITLE: Regulation of rat hepatic cytochrome P450 expression by sterol biosynthesis inhibition: inhibitors of squalene synthase are potent inducers of CYP2B expression in primary cultured rat hepatocytes and rat liver
AUTHOR(S): Kocarek, Thomas A.; Kraniak, Janice M.; Reddy, Anita B.
CORPORATE SOURCE: Institute of Chemical Toxicology, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Molecular Pharmacology (1998), 54(3), 474-484
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 57-88-5, **Cholesterol**, biological studies 79-63-0, Lanosterol 111-02-4, Squalene 9028-35-7, 3-Hydroxy-3-methylglutaryl CoA reductase 96595-04-9, Pentoxyresorufin O-dealkylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors of squalene synthase as inducers of **CYP2B** expression in primary cultured rat hepatocytes and rat liver)

L4 ANSWER 4 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998337723 MEDLINE
DOCUMENT NUMBER: 98337723 PubMed ID: 9674966
TITLE: Marked inhibition of hepatic cytochrome P450 activity in cholesterol-induced atherosclerosis in rabbits.
AUTHOR: Irizar A; Ioannides C
CORPORATE SOURCE: Molecular Toxicology Group, School of Biological Sciences, University of Surrey, Guildford, UK.
SOURCE: TOXICOLOGY, (1998 Apr 3) 126 (3) 179-93.
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ENTRY MONTH: 199808
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AB . . . and of other enzyme systems, in hepatic and extrahepatic tissues of rabbits rendered atherosclerotic by the dietary administration of 1% **cholesterol** diets for 8 weeks. Individual cytochrome P450 proteins were monitored using diagnostic substrates and immunologically in Western blot analysis. The. . . determined immunologically, no major differences were evident between the control and the atherosclerotic rabbits. In vitro studies indicated that neither **cholesterol** nor palm oil inhibited cytochrome P450 activity. The effects of **cholesterol** treatment leading to atherosclerosis on kidney, heart and lung cytochrome P450 activities were isoform- and tissue-specific; no change was evident. . . in the heart activities, but in the lung and

kidney cytochrome P450 activities were clearly modulated by the treatment with **cholesterol**. Apoprotein levels did not always parallel the changes in activities. Western blot analysis of aortic cytochromes P450 revealed that administration of **cholesterol**-rich diets enhanced **CYP2B** and CYP3A apoprotein levels. **Cholesterol** feeding to rabbits gave rise to a marked decrease in hepatic glutathione S-transferase activity but did not influence glutathione reductase. . . same treatment had no effect on catalase, glutathione peroxidase and superoxide dismutase. It is concluded that treatment of rabbits with **cholesterol**-rich diets leading to atherosclerosis gives rise to profound changes in the expression of cytochrome P450 proteins in the liver and. . .

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2: Kakizaki S, Karami S, Negishi M. Related Articles

Retinoic acids repress constitutive active receptor-mediated induction by 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene of the CYP2B10 gene in mouse primary hepatocytes.
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PMID: 11792692 [PubMed - indexed for MEDLINE]

3: Honkakoski P, Zelko I, Sueyoshi T, Negishi M. Related Articles, OMIM

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Mol Cell Biol. 1998 Oct;18(10):5652-8.
PMID: 9742082 [PubMed - indexed for MEDLINE]

4: Kawamoto T, Sueyoshi T, Zelko I, Moore R, Washburn K, Negishi M. Related Articles

Phenobarbital-responsive nuclear translocation of the receptor CAR in induction of the CYP2B gene.
Mol Cell Biol. 1999 Sep;19(9):6318-22.
PMID: 10454578 [PubMed - indexed for MEDLINE]

5: Xie W, Barwick JL, Simon CM, Pierce AM, Safe S, Blumberg B, Guzelian PS, Evans RM. Related Articles

Reciprocal activation of xenobiotic response genes by nuclear receptors SXR/PXR and CAR.
Genes Dev. 2000 Dec 1;14(23):3014-23.
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6: Ueda A, Kakizaki S, Negishi M, Sueyoshi T. Related Articles

Residue threonine 350 confers steroid hormone responsiveness to the mouse nuclear orphan receptor CAR.
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PMID: 12021388 [PubMed - indexed for MEDLINE]

7: Zelko I, Negishi M. Related Articles

Phenobarbital-elicited activation of nuclear receptor CAR in induction of cytochrome P450 genes.
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PMID: 11027630 [PubMed - indexed for MEDLINE]

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9: Muangmoonchai R, Smirlis D, Wong SC, Edwards M, Phillips IR, Shephard EA. Related Articles

Xenobiotic induction of cytochrome P450 2B1 (CYP2B1) is mediated by the orphan nuclear receptor constitutive androstane receptor (CAR) and requires steroid co-activator 1 (SRC-1) and the transcription factor Sp1.
Biochem J. 2001 Apr 1;355(Pt 1):71-8.
PMID: 11256950 [PubMed - indexed for MEDLINE]

10: Ueda A, Hamadeh HK, Webb HK, Yamamoto Y, Sueyoshi T, Afshari CA, Lehmann JM, Negishi M. Related Articles

Diverse roles of the nuclear orphan receptor CAR in regulating hepatic genes in response to phenobarbital.
Mol Pharmacol. 2002 Jan;61(1):1-6.
PMID: 11752199 [PubMed - indexed for MEDLINE]

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[Peroxisome proliferator-activated receptor (PPAR)]
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13: Columbano A, Ledda-Columbano GM, Pibiri M, Concas D, Reddy JK, Rao MS. Related Articles

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14: Smirlis D, Muangmoonchai R, Edwards M, Phillips IR, Shephard EA. Related Articles

Orphan receptor promiscuity in the induction of cytochromes p450 by xenobiotics.
J Biol Chem. 2001 Apr 20;276(16):12822-6.
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Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor.
J Biol Chem. 2002 Jan 25;277(4):2908-15.
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16: Sueyoshi T, Kawamoto T, Zelko I, Honkakoski P, Negishi M. Related Articles, Nucleotide, Protein

The repressed nuclear receptor CAR responds to phenobarbital in activating the human CYP2B6 gene.
J Biol Chem. 1999 Mar 5;274(10):6043-6.
PMID: 10037683 [PubMed - indexed for MEDLINE]

17: Moore LB, Parks DJ, Jones SA, Bledsoe RK, Consler TG, Stimmel JB, Goodwin B, Liddle C, Blanchard SG, Willson TM, Collins JL, Kliewer SA. Related Articles

Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands.
J Biol Chem. 2000 May 19;275(20):15122-7.
PMID: 10748001 [PubMed - indexed for MEDLINE]

18: Yoshinari K, Sueyoshi T, Moore R, Negishi M. Related Articles, Nucleotide, Protein

Nuclear receptor CAR as a regulatory factor for the sexually dimorphic induction of CYB2B1 gene by phenobarbital in rat livers.
Mol Pharmacol. 2001 Feb;59(2):278-84.
PMID: 11160864 [PubMed - indexed for MEDLINE]

19: Zelko I, Sueyoshi T, Kawamoto T, Moore R, Negishi M. Related Articles

The peptide near the C terminus regulates receptor CAR nuclear translocation induced by xenochemicals in mouse liver.
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PMID: 11283262 [PubMed - indexed for MEDLINE]

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Characterization of a phenobarbital-responsive enhancer module in mouse P450 Cyp2b10 gene.
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PMID: 9169466 [PubMed - indexed for MEDLINE]

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Eiris JM, Lojo S, Del Rio MC, Novo I, Bravo M, Pavon P, Castro-Gago M.
Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy.
Neurology. 1995 Jun;45(6):1155-7.

Franzoni E, Govoni M, D'Addato S, Gualandi S, Sangiorgi Z, Descovich GC, Salvioli GP.
Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs.
Epilepsia. 1992 Sep-Oct;33(5):932-5.

Thanks a lot...

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Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy

J.M. Eirís, MD; S. Lojo, PhD; M.C. Del Río, PhD; I. Novo, MD; M. Bravo, MD; P. Pavón, MD; and M. Castro-Gago, MD

Article abstract—We determined serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TGs) in 125 healthy children and in 119 children with epilepsy who had been receiving carbamazepine (58 children), phenobarbital (22 children), or valproic acid (39 children) for 7 months to 10.5 years (mean, 5.8 years). None of the variables considered was significantly correlated with time elapsed since start of treatment or with drug concentration in serum. In the groups receiving carbamazepine or phenobarbital, mean TC, HDL-C, and LDL-C levels were higher than in the control group, the differences being statistically significant for all except LDL-C in the phenobarbital group. In neither group did mean TC/HDL-C ratio or mean LDL-C/HDL-C ratio differ significantly from the corresponding control-group mean. In the group receiving valproic acid, mean TC level, mean LDL-C level, mean TC/HDL-C ratio, and mean LDL-C/HDL-C ratio were significantly lower than in the control group. In none of the treated groups did mean VLDL-C or TG level differ significantly from the corresponding control-group mean. Our results suggest, in contrast to previous reports, that the effects on the serum lipid profile of long-term treatment with hepatic-enzyme–inducing antiepileptic drugs (such as carbamazepine and phenobarbital) are probably not beneficial as regards risk of atherosclerosis-related disease. Our results additionally suggest a need for careful monitoring of serum cholesterol levels in children with epilepsy receiving carbamazepine or phenobarbital.

NEUROLOGY 1995;45:1155-1157

Childhood epilepsy often requires prolonged treatment with antiepileptic drugs (AEDs), in some cases continuing throughout the patient's life. Epidemiologic studies have indicated that mortality due to atherosclerosis-related heart disease is lower in treated epileptics than in the general population.[1,2] A number of authors have reported that treatment with hepatic-enzyme–inducing AEDs—such as carbamazepine, phenobarbital, and phenytoin—leads to increased high-density lipoprotein cholesterol (HDL-C) levels in serum.[3-9] Since the risk of coronary heart disease is positively correlated with high serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and negatively correlated with high serum levels of HDL-C and with a high ratio of serum HDL-C to serum LDL-C,[10-12] Muuronen et al[1] suggested that the lower mortality due to coronary atherosclerosis in the epileptic population may reflect increases in HDL-C levels in response to treatment with hepatic-enzyme–inducing AEDs.

Some authors have reported that hepatic-enzyme–inducing AEDs cause not only long-term increases in serum HDL-C levels but also short-term increases (over the first year of treatment) in serum levels of TC, LDL-C, and triglycerides (TGs).[13,14] Other studies have suggested that treatment with carbamazepine leads to long-term increases in all cholesterol fractions,[15] or that short-term treatment with hepatic-enzyme–inducing AEDs leads to increases in the levels of TC but not of HDL-C.[16] The literature on the effects of hepatic-enzyme–inducing AEDs on serum lipid profiles (and, by extension, on risk of atherosclerosis) is thus contradictory: it is, for example, entirely unclear whether epileptic children receiving hepatic-enzyme–inducing AEDs should follow a low-fat diet, as recommended by Franzoni et al.[16]

In the published studies on the effect of hepatic-enzyme–inducing AEDs on serum lipid profiles, the samples have mostly comprised adults[3,4,6,13,14,17,18] or adults and children together[7,19]; in only a few studies have the samples been of children alone.[15,16,20] In the work reported here, we investigated serum levels of cholesterol, cholesterol fractions, and TGs in 119 children with epilepsy who had been receiving

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Table. Basic statistics and results in each of the four groups

	Control	Carbamazepine	Phenobarbital	Valproic acid
Number of subjects, M/F	64/61	37/21	10/12	23/16
Age (yr), M/F	10.6 (2.8)/10.4 (2.9)	11.8 (2.4)/11.3 (2.7)	9.5 (3.1)/7.5 (2.5)	10.4 (2.6)/10.2 (3.3)
Duration of therapy (yr), M/F		3.7 (2.1)/3.8 (2.6)	6.2 (3.1)/5.1 (1.6)	3.3 (1.6)/3.9 (2.2)
Drug concentration in serum (μg/ml), M/F		5.5 (1.2)/6.3 (1.3)	14.3 (4.8)/12.9 (4.9)	62.2 (21.2)/57.1 (19.1)
TC (mg/dl)	172.20 (25.0)	193.56 (31.6)†	190.50 (34.5)*	153.82 (20.9)†
TGs (mg/dl)	65 (21)	69 (25)	61 (21)	58 (21)
HDL-C (mg/dl)	55.50 (13.4)	64.15 (18.1)†	63.35 (20.6)*	55.40 (15.5)
LDL-C (mg/dl)	103.80 (21.6)	114.40 (30.9)*	113.36 (32.4)	85.20 (18.0)†
VLDL-C (mg/dl)	13.8 (7.7)	13.7 (5.4)	13.6 (6.0)	11.8 (4.1)
TC/HDL-C ratio	3.26 (0.84)	3.17 (0.90)	3.18 (0.82)	2.88 (0.68)*
LDL-C/HDL-C ratio	2.01 (0.75)	1.91 (0.83)	1.91 (0.82)	1.64 (0.84)*

Numbers in parentheses are standard deviations.

* $p < 0.05$.
† $p < 0.001$.
TC Total cholesterol.
TGs Triglycerides.
HDL-C High-density lipoprotein cholesterol.
LDL-C Low-density lipoprotein cholesterol.
VLDL-C Very low-density lipoprotein cholesterol.

carbamazepine, phenobarbital, or valproic acid over a long period (mean, 5.8 years) and in 125 healthy children from the same region (Galicia, northwest Spain) and with similar diet.

Methods. Basic statistics for the four groups of subjects (carbamazepine, phenobarbital, valproic acid, and control) are listed in the table. Blood samples were taken between 8:30 and 9:30 AM after an overnight fast and stored at −40 °C until analysis. TGs and TC were determined by colorimetry with a Hitachi 747 automated analyzer (Boehringer Mannheim Diagnostics). The various cholesterol fractions were determined with a Rep Ultra-30 system (Helena Laboratories), which is based on electrophoretic separation and subsequent enzymatic quantification of cholesterol and cholesterol esters associated with each lipoprotein fraction. Student's *t* test and linear regression analysis were employed to assess the significance of the results.

Results. In the epileptic group, there was no significant correlation between serum lipid levels and age, sex, time elapsed since start of treatment, drug dosage, or drug concentration in serum. Similarly, in the control group there was no significant correlation between serum lipid levels and age or sex. Mean serum TC levels were significantly higher in the groups receiving carbamazepine (194 ± 32 mg/dl) or phenobarbital (191 ± 35 mg/dl) than in the control group (172 ± 25 mg/dl); mean serum TC level in the group receiving valproic acid (154 ± 21 mg/dl), on the other hand, was significantly lower than in the control group (table). Serum TC level exceeded 200 mg/dl in 41% of the subjects receiving carbamazepine and 50% of the subjects receiving phenobarbital, but in only 12% of control-group subjects; by contrast, TC level did not exceed 200 mg/dl in any of the subjects receiving valproic acid. Mean HDL-C levels were significantly higher in the groups receiving carbamazepine (64 ± 18 mg/dl) or phenobarbital (63 ± 21 mg/dl) than in the control group (56 ± 13 mg/dl); however, mean HDL-C level in the group receiving valproic acid (55 ± 16 mg/dl) did not differ significantly from that in the control group (table). Mean LDL-C level was significantly higher in the group receiving carbamazepine (114 ± 31 mg/dl) and nonsignificantly higher in the group receiving phenobarbital (113 ± 32 mg/dl) than in the control group (104 ± 22 mg/dl); mean LDL-C level in the group receiving valproic acid (85 ± 18 mg/dl) was significantly lower than in the control group (table). There were no significant differences in mean TG level or mean very low-density liproprotein cholesterol level (table) between the control group and any of the treated groups. Mean LDL-C/HDL-C ratio was significantly lower in the group receiving valproic acid (1.64 ± 0.84) than in the control group (2.01 ± 0.75), but did not differ significantly from the control group in the other two treated groups (table). Likewise, mean TC/HDL-C ratio was significantly lower in the group receiving valproic acid (2.88 ± 0.68) than in the control group (3.26 ± 0.84) and again did not differ significantly from the control group in the other two treated groups (table).

Discussion. Our sample consisted of 119 children with epilepsy who were taking AEDs for 7 months to 10.5 years; only four patients—two in the carbamazepine group and two in the valproic acid group—were treated for less than 1 year. In all cases, the treatment was appropriate for the control of epilepsy (mean time elapsed since last attack: 61 ± 34 months) and serum levels of the drug were within the corresponding therapeutic range. Mean TC, HDL-C, and LDL-C levels were all higher in the carbamazepine- and phenobarbital-treated groups than in the control group (the differences being statistically significant except for LDL-C in the phenobarbital group), although in neither case did mean LDL-C/HDL-C ratio or mean

TC/HDL-C ratio differ significantly from the corresponding control-group mean.

Excepting LDL-C and TC in the phenobarbital group, our results constitute statistically significant confirmation of the findings of Heldenberg et al[15] and are in contrast to reports that TC and LDL-C levels are high only during the initial period of treatment.[9,14,17] Equally, our results do not support the assertion that TC levels rise as a result of increased LDL-C levels only,[16] but suggest that the increase in TC is due to both LDL-C and HDL-C.

In the group treated with valproic acid (which does not induce hepatic enzymes), mean TC and LDL-C levels, mean LDL-C/HDL-C ratio, and mean TC/HDL-C ratio were significantly lower than in the control group. This is in accordance with previous studies,[15,16,19] although in one study[20] there were no significant differences between treated and control groups.

The Committee on Nutrition of the American Academy of Pediatrics (AAP) has classified serum TC levels in the range of 170 to 199 mg/dl as "borderline" and levels in excess of 200 mg/dl as "high."[21] We found that serum TC level exceeded 200 mg/dl in 41% of carbamazepine-treated children and in 50% of phenobarbital-treated children (as opposed to 12% of control-group children). This suggests a need for careful monitoring of serum lipid levels in children with epilepsy receiving these drugs. The AAP statement[21] points out that TC is an imperfect predictor of the risk of coronary vascular disease; thus, in children with high TC levels, LDL-C levels should also be determined. LDL-C levels in the range of 110 to 129 mg/dl are defined by the AAP as "borderline," while levels in excess of 129 mg/dl are defined as "high." In our study, LDL-C level exceeded 129 mg/dl in 29% of carbamazepine-treated children and 23% of phenobarbital-treated children (as opposed to only 9% of control-group children), but in only one valproic acid-treated child was LDL-C level high.

The normal ranges for serum cholesterol and its fractions are wide and appear to be dependent upon sex and age. The effects of hepatic-enzyme–inducing AEDs on serum lipid profile (and thus on risk of atherosclerosis) seem to be accurately evaluated only with reference to pretreatment levels in specific patients. Long-term prospective studies are required to clarify the effects of hepatic-enzyme–inducing AEDs on lipid metabolism in children. Despite the need for longer-term research, the results of the present study clearly indicate that serum lipid profiles should be carefully monitored in children receiving carbamazepine or phenobarbital. If analysis reveals high TC or LDL-C levels in serum, a low-fat diet[21] may be indicated. Serum lipid levels in children receiving valproic acid do not require special attention.

References

1. Muuronen A, Kaste M, Nikkilä EA, Tolppanen EM. Mortality from ischaemic heart disease among patients using anticonvulsive drugs: a case-control study. BMJ 1985;291:1481-1483.
2. Livingston S. Phenytoin and serum cholesterol [letter]. BMJ 1976;1:586.
3. Nikkilä EA, Kaste M, Ehnholm Ch, Viikari J. Elevation of high-density lipoprotein in epileptic patients treated with phenytoin. Acta Med Scand 1978;204:517-520.
4. Luoma PV, Myllylä VV, Sotaniemi EA, Lehtinen IA, Hokkanen EJ. Plasma high-density lipoprotein cholesterol in epileptics treated with various anticonvulsants. Eur Neurol 1980;19:67-72.
5. Luoma PV, Sotaniemi EA, Pelkonen RO, Myllylä VV. Plasma high-density lipoprotein cholesterol and hepatic cytochrome P-450 concentrations in epileptics undergoing anticonvulsant treatment. Scand J Clin Lab Invest 1980;40:163-167.
6. Luoma PV, Myllylä VV, Hokkanen E. Relationship between plasma high-density lipoprotein cholesterol and anticonvulsant levels in epileptics. J Cardiovasc Pharmacol 1982;4:1024-1027.
7. O'Neill B, Callaghan N, Stapleton M, Molloy W. Serum elevation of high density lipoprotein (HDL) cholesterol in epileptic patients taking carbamazepine or phenytoin. Acta Neurol Scand 1982;65:104-109.
8. Luoma PV. Microsomal enzyme induction, lipoproteins and atherosclerosis. Pharmacol Toxicol 1988;62:243-249.
9. Luoma PV, Reunanen MI, Sotaniemi EA. Changes in serum triglyceride and cholesterol levels during long-term phenytoin treatment for epilepsy. Acta Med Scand 1979;206:229-231.
10. Berenson GS, Srinivasan SR, Nicklas TA, Webber LS. Cardiovascular risk factors in children and early prevention of heart disease. Clin Chem 1988;34:B115-B122.
11. Newman WP, Freedman DS, Voors AW. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa heart study. N Engl J Med 1986;314:138-144.
12. Newman WP, Wattigney W, Berenson GS. Autopsy studies in United States children and adolescents. Relationship of risk factors to atherosclerosis lesions. Ann N Y Acad Sci 1991;623:16-25.
13. Luoma PV, Sotaniemi EA, Arranto AJ. Serum LDL cholesterol, the LDL/HDL cholesterol ratio and liver microsomal enzyme induction evaluated by antipyrine kinetics. Scand J Clin Lab Invest 1983;43:671-675.
14. Isojärvi JIT, Pakarinen AJ, Myllylä VV. Serum lipid levels during carbamazepine medication: a prospective study. Arch Neurol 1993;50:590-593.
15. Heldenberg D, Harel S, Holtzman M, Levtow O, Tamir I. The effect of chronic anticonvulsant therapy on serum lipids and lipoproteins in epileptic children. Neurology 1983;33:510-513.
16. Franzoni E, Govoni M, D'Addato S, et al. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs. Epilepsia 1992;33:932-935.
17. Brown DW, Ketter TA, Crumlish J, Post RM. Carbamazepine-induced increases in total serum cholesterol: clinical and theoretical implications. J Clin Psychopharmacol 1992;12:431-437.
18. Pelkonen R, Fogelholm R, Nikkilä EA. Increase in serum cholesterol during phenytoin treatment. BMJ 1975;283:85.
19. Calandre EP, Rodriguez-López C, Blazquez A, Cano D. Serum lipids, lipoproteins and apolipoproteins A and B in epileptic patients treated with valproic acid, carbamazepine or phenobarbital. Acta Neurol Scand 1991;83:250-253.
20. Reddy MN. Effect of anticonvulsant drugs on plasma total cholesterol, high-density lipoprotein cholesterol, and apolipoproteins A and B in children with epilepsy. Proc Soc Exp Biol Med 1985;180:359-363.
21. American Academy of Pediatrics, Committee on Nutrition. Statement on cholesterol. Pediatrics 1992;90:469-473.

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Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants.

Verrotti A, Domizio S, Angelozzi B, Sabatino G, Morgese G, Chiarelli F.

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OBJECTIVE: To assess the effect of long-term treatment of phenobarbital, carbamazepine and sodium valproate on serum lipids and lipoproteins in epileptic children. METHODOLOGY: One hundred and fourteen (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different antiepileptic drugs were studied. The patients were subdivided into three groups according to their therapy: (i) carbamazepine (35 patients); (ii) phenobarbital (34 patients); and (iii) sodium valproate (45 patients). One-hundred healthy sex- and age-matched children served as controls. Lipids and lipoprotein profile were evaluated before the beginning of the anticonvulsant therapy and after at least 2.5 years. In the patients receiving phenobarbital, we re-evaluated 12 children (seven male, five female) at the end of therapy. RESULTS: The children receiving phenobarbital showed high levels of serum total cholesterol and low-density lipoprotein (LDL) cholesterol and low levels of triglycerides, while children treated with carbamazepine had high levels of total cholesterol, triglycerides, LDL and high-density lipoprotein (HDL) cholesterol. Children treated with valproate had low triglycerides and LDL cholesterol levels with high levels of HDL cholesterol. The patients treated with phenobarbital showed a normalization of all parameters after the end of therapy. CONCLUSIONS: Anticonvulsant drugs significantly modify serum lipids and lipoproteins in epileptic children. The changes due to phenobarbital seem to be transient.

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Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy.

Eiris JM, Lojo S, Del Rio MC, Novo I, Bravo M, Pavon P, Castro-Gago M.

Department of Pediatrics, Hospital General de Galicia, Santiago de Compostela, Spain.

We determined serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TGs) in 125 healthy children and in 119 children with epilepsy who had been receiving carbamazepine (58 children), phenobarbital (22 children), or valproic acid (39 children) for 7 months to 10.5 years (mean, 5.8 years). None of the variables considered was significantly correlated with time elapsed since start of treatment or with drug concentration in serum. In the groups receiving carbamazepine or phenobarbital, mean TC, HDL-C, and LDL-C levels were higher than in the control group, the differences being statistically significant for all except LDL-C in the phenobarbital group. In neither group did mean TC/HDL-C ratio or mean LDL-C/HDL-C ratio differ significantly from the corresponding control-group mean. In the group receiving valproic acid, mean TC level, mean LDL-C level, mean TC/HDL-C ratio, and mean LDL-C/HDL-C ratio were significantly lower than in the control group. In none of the treated groups did mean VLDL-C or TG level differ significantly from the corresponding control-group mean. Our results suggest, in contrast to previous reports, that the effects on the serum lipid profile of long-term treatment with hepatic-enzyme-inducing antiepileptic drugs (such as carbamazepine and phenobarbital) are probably not beneficial as regards risk of atherosclerosis-related disease. Our results additionally suggest a need for careful monitoring of serum cholesterol levels in children with epilepsy receiving carbamazepine or phenobarbital.

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Neurology. 1995 Jun;45(6):1155-7.

Franzoni E, Govoni M, D'Addato S, Gualandi S, Sangiorgi Z, Descovich GC, Salvioli GP.
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Thanks a lot...

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Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants

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Objective: To assess the effect of long-term treatment of phenobarbital, carbamazepine and sodium valproate on serum lipids and lipoproteins in epileptic children.

Methodology: One hundred and fourteen (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different antiepileptic drugs were studied. The patients were subdivided into three groups according to their therapy: (i) carbamazepine (35 patients); (ii) phenobarbital (34 patients); and (iii) sodium valproate (45 patients). One-hundred healthy sex- and age-matched children served as controls. Lipids and lipoprotein profile were evaluated before the beginning of the anticonvulsant therapy and after at least 2.5 years. In the patients receiving phenobarbital, we re-evaluated 12 children (seven male, five female) at the end of therapy.

Results: The children receiving phenobarbital showed high levels of serum total cholesterol and low-density lipoprotein (LDL) cholesterol and low levels of triglycerides, while children treated with carbamazepine had high levels of total cholesterol, triglycerides, LDL and high-density lipoprotein (HDL) cholesterol. Children treated with valproate had low triglycerides and LDL cholesterol levels with high levels of HDL cholesterol. The patients treated with phenobarbital showed a normalization of all parameters after the end of therapy.

Conclusions: Anticonvulsant drugs significantly modify serum lipids and lipoproteins in epileptic children. The changes due to phenobarbital seem to be transient.

Many studies, mainly carried out on adult populations, have provided the evidence that there is a significant influence of long-term antiepileptic drugs (AED) therapy on total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and apolipoproteins levels.[1–7] The few studies in the paediatric literature on the effects of the antiepileptic therapy on lipid metabolism are limited in terms of patient numbers and show contradictory results.[8–11] For example, Hendelberg *et al.*[11] found that HDL-cholesterol is very high in children receiving sodium valproate and carbamazepine and that children treated with phenobarbital and sodium valproate showed lower TG levels than controls, while Franzoni *et al.*[8] did not find any significant abnormalities in serum lipids. The patients studied often received a combination of antiepileptic drugs (AED), for different periods of time and there are no prospective studies.

Our study was conducted in order to investigate the possible changes in serum lipids and lipoprotein levels in a large number of epileptic children receiving monotherapy for a long period of time and to investigate the reversibility of the effect of AED on lipids after the end of the therapy.

METHODS

We studied 114 (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different AED. The patients were subdivided into three groups according to their therapy: (i) group A, phenobarbital (34 patients, age range 13.4–18.1 years); (ii) group B, carbamazepine (35 patients, age range 10.0–19.6) and (iii) group C, sodium valproate (45 patients, age range 11.9–18.0). The group A children suffered from generalized tonic-clonic and simple partial seizures, while the large majority of patients of the group B showed complex partial seizures. The patients with tonic-clonic absence and/or minor motor seizures were treated with sodium valproate (group C). Treatment always began with one drug, its dosage being increased until seizures were controlled without developing toxicity. If a second drug was added the patient was excluded from the study. None of the patients had been treated with adrenocorticotropic hormone (ACTH). Gender and duration of treatment were similar in the three groups.

We evaluated the lipids and lipoprotein profile before anticonvulsant therapy and after at least 2.5 years. In the group of patients receiving phenobarbital, we have been able to re-evaluate 12 children (7 male, 5 female) who stopped their therapy after a period of mean 1.2 ± 0.5 years (range 1.0–1.7 years).

One-hundred healthy sex-matched children with range of age from 10.0 to 19.6 years, served as controls. The control group had never received any AED or other drugs that can affect lipids and lipoprotein metabolism and had never suffered from endocrinological, metabolical or renal disease. None of the subjects followed dietary restriction. The patients and the controls lived in the same area with the same dietary habits. The patients studied did not change significantly their physical exercise and dietary habits during the study. There was no difference in physical activity and diet between the epileptic patients and the controls.

The diet of the children studied (patients and controls) was

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analysed by a questionnaire: each patient was interviewed and invited to fill out a questionnaire concerning the kind and amount of food consumed every day in the week preceding the interview. Both patients and controls estimated the size and the amount of food eaten by units of weight, volume or household measure or with the aid of graduated food models. Data on home food and food preparation were also collected from the parents by a questionnaire.

All plasma levels of AED were within the therapeutic range: carbamazepine 7.0 ± 1.9 μg/mL, sodium valproate 62.4 ± 19.4 μg/mL, phenobarbital 17.5 ± 2.7 μg/mL. All blood samples were drawn fasting in the morning and before the first day drug-dose. Lipids were measured in serum and the HDL containing supernatant after precipitation of apo B containing lipoproteins. Cholesterol and triglycerides were measured enzymatically, as previously described[12] using automated methods. Low-density lipoprotein cholesterol was calculated by the Friedewald formula.

High-density lipoprotein was isolated by ultracentrifugation.[13,14] The background density of plasma was adjusted to 1063 gL^{-1} by adding a sodium chloride-potassium bromide solution. The infranatants were obtained by tube slicing after ultracentrifugation at 100 000 × g for 48 h (L8M55 ultracentrifugation with 50.3 Ti Rotor; Beckman, Richmond, VA, USA).[15]

In view of the possibility that lipoprotein (a) might interfere with the isolation of HDL by ultracentrifugation, HDL was also isolated by precipitation of other lipoproteins, including lipoprotein (a), with sodium phosphotungstate and magnesium chloride.[16,17] Total serum apolipoprotein A1 and B concentrations were determined by immunoelectrophoresis using goat-antiserum (Immuno, Dunton Green, Kent, UK). The within-batch coefficient of variation of the assay was 5.4%.

Serum lipoprotein (a) concentrations were measured, using a two-site radioimmunometric assay (Pharmacia Diagnostics, Sweden). After hydrolysis and dilution, the serum sample was incubated with an excess of ^{125}I-labelled anti-apo (a) monoclonal antibody and a different monoclonal antibody coupled to microsepharose. Antibody-antigen complexes were separated from unbound ^{125}I by centrifugation and their radioactivity was measured. A standard curve was constructed for each assay. The within-assay coefficient of variation was 6%. Results are expressed in terms of the Pharmacia standard and are in U/dL.

Statistical methods

Results are expressed as mean ± SD or medians and ranges for data not normally distributed; P values less than 0.05 were considered significant. All variables measured have been checked for normality and adjusted using Duncan's method, as appropriate. The comparison of data among groups was performed by Wilcoxon's rank sum test and by paired and unpaired Student's t-test. Moreover, Spearman's rank correlation coefficient was performed.

RESULTS

The mean serum levels of lipids and lipoproteins of the three groups of patients and controls before the beginning of the therapy and during treatment are given in Table 1. Before the treatment, all the children showed similar values to those of the control group. The data of the patients after at least 2.5 years of treatment are shown in Table 1.

The children receiving phenobarbital showed high levels of serum TC and LDL cholesterol and low levels of TG, while group B children had high levels of TC, TG, LDL and HDL cholesterol; finally, children treated with valproate (group C) had low TG and LDL cholesterol levels with high levels of HDL cholesterol.

There was no significant difference in the levels of serum apolipoproteins A1 and B between the three groups of patients and controls. In epileptic patients, no significant correlation was found between AED plasma concentrations and lipids and lipoproteins levels.

There was no difference in growth between the groups of patients. All subjects showed a body mass index between 10th to 90th percentile. In order to evaluate liver function, serum transaminases and alkaline phosphatase concentrations were assessed: all patients showed normal values.

The values of lipids and lipoproteins of children who discontinued phenobarbital were compared with the values during treatment. After the end of therapy, all the values were similar to those observed before beginning therapy.

DISCUSSION

Our study shows that even in children and adolescents receiving AED it is possible to find significant abnormalities in the serum lipids and lipoprotein profile. These data are in agreement with previous studies performed in adult epileptic patients.[1-7] In fact, Nikkila *et al.*[1] reported an increase in HDL cholesterol and TG levels, and Berlit *et al.*[3] found a significant increase of all lipid fractions in adult patients receiving various AED, while others[2,10] reported high TC levels in patients treated with phenytoin. Patient groups were not always clearly defined and very often they received AED polytherapy. In the present study all the epileptic children were treated with monotherapy for at least 2.5 years. Consequently, it has been possible to evaluate the effect of the single AED on the lipid parameters after a long period of time.

The baseline lipids and lipoproteins serum levels in our children indicate that changes in concentration do not result from the convulsive disorder itself, but are the consequence of the AED administration, although no significant correlation was found between AED plasma concentrations and serum lipids and lipoproteins levels.

We found a significant increase of TC and LDL cholesterol in children in treatment with phenobarbital. This is in contrast to previous studies[8,9] but, in agreement with others.[3,11] It is possible that phenobarbital, as with other drugs that may cause hypertrophy of liver microsomes, can induce a proliferation of the endoplasmatic reticulum, which is probably the site in liver cells where the lipoprotein lipids are synthesized and organized to particles. This reticulum can be the main subcelluler structure stimulated by phenobarbital with consequent changes in lipoproteins levels. This hypothesis is supported by some biochemical studies[18-21] which demonstrated that barbiturates cause a marked increase in the enzymes, protein and lipid content of the hepatic smooth endoplasmic reticulum and can modify many microsomial and mitochondrial enzymes.

Children treated with carbamazepine showed high levels of TC, TG and HDL cholesterol; these data are in agreement with those reported by Isojarvi *et al.*[5] who demonstrated this in adult patients. Other authors[4,6,10,11] found these abnormalities in patients treated with carbamazepine, while others did not

Table 1 Serum lipids of the three groups of patients (before and during treatment) and in controls

	Controls	Phenobarbital	Patients before treatment Carbamazepine	Sodium valproate	Phenobarbital	Patients after treatment Carbamazepine	Sodium valproate
Number of patients (M/F)	100 (50/50)	34 (16/18)	35 (17/18)	45 (22/23)	34 (16/18)	35 (17/18)	45 (22/23)
Age (years)	15.6 ± 5.9	15.7 ± 2.4	15.2 ± 5.2	14.7 ± 3.3	20.6 ± 2.7	19.8 ± 5.2	19.8 ± 5.9
Dosage (mg/kg)					3.2 ± 0.5	16.7 ± 8.2	52.7 ± 12.9
Duration of treatment (year)					3.9 ± 0.7	2.5 ± 2.7	3.1 ± 2.9
Serum cholesterol (mmol/L)	4.46 ± 0.92	4.47 ± 0.73	4.45 ± 0.81	4.48 ± 0.67	5.6 ± 1.1†	5.71 ± 1.52†	4.67 ± 1.14
Serum triglycerides (mmol/L)	1.21 ± 0.42	1.23 ± 0.21	1.2 ± 0.5	1.22 ± 0.31	1.01 ± 0.30*	1.49 ± 0.62*	1.02 ± 0.67*
LDL cholesterol (mmol/L)	2.31 ± 0.50	2.32 ± 0.61	2.33 ± 0.32	2.3 ± 0.4	2.56 ± 0.61*	2.61 ± 0.54*	2.05 ± 0.83†
VLDL (mmol/L)	0.52 ± 0.21	0.51 ± 0.92	0.5 ± 0.40	0.53 ± 0.10	0.55 ± 0.81	0.53 ± 0.86	0.56 ± 0.41
HDL (mmol/L)	1.31 ± 0.46	1.32 ± 0.30	1.33 ± 0.21	1.34 ± 0.14	1.42 ± 0.32	2.01 ± 0.60†	1.94 ± 0.52†
Apolipoprotein A1 (mmol l^{-1})	$4.9\ 10^{-2} \pm 2\ 10^{-3}$	$5.1\ 10^{-2} \pm 2\ 10^{-3}$	$4.8\ 10^{-2} \pm 2\ 10^{-3}$	$5.0\ 10^{-2} \pm 2\ 10^{-3}$	$4.7\ 10^{-2} \pm 2\ 10^{-3}$	$5.0\ 10^{-2} \pm 2\ 10^{-3}$	[illegible]
Apolipoprotein B (mmol l^{-1})	$1.9\ 10^{-3} \pm 1.3\ 10^{-4}$	$1.8\ 10^{-3} \pm 1.2\ 10^{-4}$	$1.7\ 10^{-3} \pm 1.4\ 10^{-4}$	$1.85\ 10^{-3} \pm 1.25\ 10^{-4}$	$1.7\ 10^{-3} \pm 1.3\ 10^{-4}$	$1.7\ 10^{-3} \pm 1.5\ 10^{-4}$	[illegible]
Apo (a)	81.3 (16–790)	87.8 (12–776)	89.1 (14–781)	83.1 (14–910)	80.1 (18–904)	94.7 (18–902)	84.4 (19–901)

*$P < 0.05$ patients *vs* controls; †$P < 0.01$ patients *vs* controls; M, male; F, female; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein.

confirm these findings.[8] It is possible that these changes can be due to an increase in gamma-glutamyltransferase activity, sometimes reported elevated in patients treated with this AED.[2] In our study, we evaluated only transaminases and alkaline phosphatase.

Patients treated with sodium valproate showed a decrease of TG and LDL cholesterol, with an increase of HDL. It is possible that biochemical hepatic injury, demonstrated recently,[20,22] can be the cause of these changes. Our data are in agreement with those of Heldenberg[11] but not with those of Zeitlhofer[4] who found a significant decrease in apoliporoprotein A1 and in apolipoprotein B. This latter study was of adults with a short duration of treatment (6 months). In another study[8] TC levels were significantly increased by carbamazepine and phenobabital, while valproate showed a mild but significant decrease in comparison to the levels of controls.

The differences between our results and those of others can be explained by the different ages of population studied, prospective *vs* retrospective analysis, one or more antiepileptic drugs received and different follow-up periods. In particular, frequently, only adult patients have been studied,[3–6] in another study,[8] performed on paediatric patients, the authors described the mean values of plasma lipids in children receiving antiepileptic drugs of any kind. Moreover, many previous studies[1–3,5,6,8,9,11] did not study the changes of apolipoproteins which have been analysed in our research. Finally, to best of our knowledge, this is the first paper reporting a study of lipids and lipoproteins in a significant number of patients receiving a single drug. We found that all the AED studied can interfere with lipid metabolism in monotherapy.

Finally, we have had the opportunity to re-evaluate a small group of patients receiving phenobarbital after the discontinuation of their therapy. All patients showed a complete normalization of the abnormalities found during therapy; our study suggests that the changes observed during the therapy are transient, and that they reverse after the end of the therapy without any permanent modification of lipid metabolism.

In conclusion, this study confirms that carbamazepine, phenobarbital and sodium valproate can modify the serum lipids and lipoprotein levels in a long term treatment on a paediatric population.

Although these changes of lipids and lipoproteins seem to be mild, it is not clear if these changes can increase the risk of atherosclerosis; an epidemiological study, performed on a large group of patients receiving antiepileptic drugs could be useful to solve this question. Antiepileptic drugs should be added to the list of drugs that may affect lipid concentration and we suggest that children who receive these drugs should be advised to follow a normocaloric diet, with a low percentage of saturated lipids.

REFERENCES

1 Nikkila EA, Kaste M, Ehnholm C, Viikari J. Elevation of high-density lipoprotein in patients treated with phenytoin. *Acta Med. Scand.* 1978; **204**: 517–20.

2 Pita Calandre EP, Sinues Porta B, Garcia de la Calzada D. The effect of chronic phenytoin treatment on serum lipid profile in adult epileptic patients. *Epilepsia* 1992; **33**: 154–7.

3 Berlit P, Krause KH, Heuk CC, Schellenberg B. Serum lipids and anticonvulsants. *Acta Neurol. Scand.* 1982; **66**: 328–34.

4 Zeitlhofer J, Doppelbauer A, Tribl G, Leitha T, Deecke L. Changes

of serum lipid pattern during long-term anticonvulsant treatment. *Clin. Invest.* 1993; **71**: 572–8.

5 Isojarvi JI, Pakarinen AJ, Myllyla VV. Serum lipid levels during carbamazepine medication. A prospective study. *Arch. Neurol.* 1993; **50**: 590–3.

6 Brown DW, Ketter TA, Crumlish J, Post RM. Carbamazepine-induced increases in total cholesterol: clinical and theoretical implications. *J. Clin. Psychopharmacol.* 1992; **12**: 431–7.

7 McKenney JM, Petrizzi KS, Briggs GC, Wright JT Jr. The effect of low-dose phenytoin on high-density lipoprotein cholesterol. *Pharmacotherapy* 1992; **12**: 183–8.

8 Franzoni E, Govoni M, D'Addato S *et al*. Total cholesterol, high-density lipoprotein cholesterol and triglycerides in children receiving antiepileptic drugs. *Epilepsia* 1992; **33**: 932–5.

9 Pelkonen R, Fogelholm R, Nikkila EA. Increase in serum cholesterol during phenytoin treatment. *BMJ* 1975; **4**: 85–8.

10 Reddy MN. Effects of anticonvulsant drugs on plasma total cholesterol, high density lipoprotein cholesterol, and apolipoprotein A and B in children with epilepsy. *Proc. Soc. Exp. Biol. Med.* 1985; **180**: 359–63.

11 Heldenberg D, Harel S, Holtzman M, Levtow O, Tamir I. The effect of chronic anticonvulsant therapy on serum lipids and lipoproteins in epileptic children. *Neurology* 1983; **33**: 510–12.

12 Verrotti A, Chiarelli F, Morgese G. Influence of puberty on lipids and lipoprotein profile in children with Type I diabetes mellitus. *Acta Diabetol.* 1995; **32**: 102–105.

13 Winocour PH, Bhatnagar D, Ishola M, Arrol S, Durrington PN. Lipoprotein (a) and microvascular disease in type 1 (insulin-dependent) diabetes. *Diabetic Med.* 1991; **8**: 922–7.

14 Havel RJ, Eder HA, Bragdon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in normal serum. *J. Clin. Invest.* 1995; **34**: 1345–53.

15 Durrington PN. Serum high density lipoprotein cholesterol subfractions in type 1 (insulin-dependent) diabetes mellitus. *Clin. Chim. Acta* 1982; **120**: 21–8.

16 Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *J. Lipid Res.* 1970; **11**: 583–95.

17 Kostner GM. Apolipoprotein A and lipoproteins of human plasma: significance in health and in disease. *Adv. Lipid Res.* 1983; **20**: 1–43.

18 Ginsberg RL, Garnick MB. Effect of phenobarbital on biliary lipid metabolism in normal man. *Gastroenterology* 1977; **72**: 1221–7.

19 Sharp HL, Mirkin BL. Effect of phenobarbital on hyperbilirubinemia, bile acid metabolism, and microsoma enzyme activity in chronic intrahepatic cholestasis of childhood. *J. Pediatr.* 1972; **81**: 116–26.

20 Rall TW, Schleifer LS. Drugs effective in the therapy of epilepsies. In Goodman and Gilman's, *The phramacological basis of therapeutics*. Macmillan Publishing Co., Inc, New York. 1995; 549–89.

21 Miller NE, Nestel PJ. Altered bile acid metabolism during treatment with phenobarbitone. *Clin. Sci. Mol. Med.* 1973; **45**: 257–61.

22 Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ. Effect of valproic acid on hepatic function. *Neurology* (Minneap) 1978; **28**: 961–4.